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EDITORIALS

PCSK9 inhibitors for hypercholesterolaemia

New drugs, old problems

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Statins (hydroxymethyl-glutaryl coenzyme A reductase inhibitors) reduce “bad” low density lipoprotein (LDL) cholesterol concentrations and cardiovascular risk. So too, do better diet and more exercise, which together almost halve rates of coronary event rates when compared with an “unfavourable lifestyle.”³ For some people, though, statins and other medicines cause unacceptable adverse effects or are inadequate to control LDL cholesterol even when combined with lifestyle changes.^{4,5} People with familial hypercholesterolaemia have particularly high concentrations of LDL cholesterol, and a new generation of drugs promises to help control this.

The drugs derived from the discovery that a few people with very low LDL cholesterol concentrations have gene mutations that cause loss of function of the enzyme PCSK9 (proprotein convertase-subtilisin/kexin type 9).^{6,7} LDL receptors on the surface of hepatocytes bind circulating LDL cholesterol and are then endocytosed. Within the cell, receptors are either recycled or degraded. We now know that PCSK9 switches this process towards degradation, and if PCSK9 is inhibited, more LDL receptors are recycled to the cell surface, where they can take up more LDL cholesterol.

This mechanistic insight has led to two newly licensed PCSK9 inhibitors, alirocumab and evolocumab. Both drugs are monoclonal antibodies, given by subcutaneous injection every two to four weeks. They significantly reduce LDL cholesterol concentrations compared with placebo, whether used alone or added to standard therapy.⁸⁻¹¹ Average concentration fell about 60% from around 3.15 mmol/L (120 mg/L) at baseline to around 1.3 mmol/L (50 mg/L) in two large, industry sponsored trials lasting up to 78 weeks. Most trial participants were already taking statins and a few were taking ezetimibe or other drugs (see supplementary table on bmj.com)^{10,11}

The primary outcome in the alirocumab study was change in LDL cholesterol concentration from baseline.¹¹ This was a secondary outcome in the evolocumab study, in which adverse events were the primary outcome.¹⁰ Since this was an open label extension of 12 earlier studies, however, participants were already known to tolerate evolocumab.

The National Institute for Health and Care Excellence recommends the new drugs for primary and secondary prevention in people with primary heterozygous familial hypercholesterolaemia whose LDL cholesterol concentrations are persistently above 5.0 mmol/L (primary prevention) or 3.5 mmol/L (secondary prevention).^{8,9} In non-familial hypercholesterolaemia or mixed dyslipidaemia the drugs are recommended only as secondary prevention for patients with a high or very high risk of cardiovascular disease and LDL cholesterol concentrations above defined thresholds after the maximum dose of other drugs has been reached or when further titration is limited by intolerance.^{8,9}

Clinical questions

The reductions in LDL cholesterol are impressive, but there are important gaps in our knowledge. Firstly, we cannot be sure that reductions in LDL cholesterol will be associated with better clinical outcomes. After all, fibrates, torcetrapib, and extended release niacin-laropirant reduced LDL cholesterol concentration but not overall mortality.¹²⁻¹⁵ Relevant trials of the PCSK9 inhibitors are due to report in 2017-18.

Secondly, the people with the greatest need for LDL cholesterol reduction are those with familial hypercholesterolaemia. In heterozygous familial hypercholesterolaemia, which affects about 1 in 500 of people with European heritage,¹² LDL cholesterol reductions of some 60% are reported.¹⁶ However, in patients with the much rarer and more serious homozygous form, LDL receptors are defective or absent, and the inhibitors therefore have considerably smaller effects, and sometimes none.¹⁷

Furthermore, treatments with PCSK9 inhibitors will require a lifetime of injections, but we have information on fewer than 1000 patients exposed for 18 months or longer.^{18,19} Few patients younger than 18 or older than 75 were included in the studies, and pregnant women and people with type 1 diabetes, severe renal or liver problems, hepatitis C or HIV infection were unrepresented.

Although people with very low LDL cholesterol concentrations because of mutations in PCSK9 have low rates of cardiovascular disease, the long term effects of using bioengineered drugs to

inhibit the enzyme are unknown. Both agents are immunogenic and can cause injection site and hypersensitivity reactions. Pfizer halted development of bococizumab, another monoclonal PCSK9 antibody, because its immunogenicity often led to hypersensitivity reactions and loss of efficacy.²⁰

Neuropsychiatric and cognitive effects have been described but remain uncharacterised. Other adverse effects may emerge only with time.

The clinical trials, then, show that PCSK9 inhibitors reduce LDL cholesterol concentration in the short term, but we are still uncertain about the long term outcomes or the nature and frequency of harms. By contrast, statins used in secondary prevention undoubtedly lower the risk of further cardiovascular events and cut all-cause mortality by about 15%.²¹ Their adverse effects are well established. Serious reactions such as significant rhabdomyolysis are rare, although statins may increase the risk of diabetes.²² Generic statins are also inexpensive. The maximum dose of generic atorvastatin costs less than £1 (€1; \$1.2) a week in England; PCSK9 inhibitors cost 100 times more.

The PCSK9 inhibitors are a seductive example of 21st century medicine, using monoclonal antibody technology to exploit a fascinating genetic observation and careful physiological analysis. There are other inhibitors in the pipeline, including inclisiran,²³ a small interfering RNA that reduced PCSK9 synthesis and LDL cholesterol concentration in volunteers without hypercholesterolaemia in a phase I trial.

Evolocumab and alirocumab, however, have been licensed on the basis of a surrogate biochemical measure, rather than clinically relevant outcomes. For now, NICE is right to limit the use of these expensive medicines to highly selected subgroups. Their clinical efficacy and long term safety remain uncertain.

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